UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
07/943,246	09/10/92	[illegible]	[illegible]

EXAMINER

18N2/1021

FOLEY & LARDNER
SUITE 500
3000 K ST N.W.
WASHINGTON DC 20007-5109

ART UNIT	PAPER NUMBER
1819	38

DATE MAILED: 10/21/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on July 18, 1997

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-4, 6-9, 11, 12, 14 and 16-24 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-4, 6-9, 11, 12, 14 and 16-24 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 16, 25 and 37
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Applicant's arguments filed July 18, 1997 in paper no. 36 have been fully considered but they are not persuasive. The amendment has been entered.

The entry on the 1449 filed June 21, 1996 "European Search Report" is not in conformance as the search report is not reference as defined in MPEP 609. Applicant should indicate those articles on the search report on the 1449.

Claims 17,20,21 and 24 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transgenic mice, rats, rabbits, pigs, sheep and goats, does not reasonably provide enablement for transgenic cows for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's species claim to transgenic cows for the production of any protein in the mammary gland for eventual isolation from the cow's milk is not enabled by the disclosure, nor are there sufficient teachings in the art for the production of such a transgenic cow that the specification does not have to provide guidance for this species.

Applicant argues that declarant Bondioli stated (declaration filed December 20, 1996) the present specification supports the production of transgenic cows (paragraph 2). Applicant argues that the declarant stated that the major breakthrough was the centrifugation of bovine oocytes prior to microinjection. Applicant argues that declarant Bondioli is an expert in the field and stated that the state of the art at the time of filing would have enabled the artisan to produce a transgenic cow expressing a transgene under the control of the long WAP promoter. Applicant argues that declarant Bondioli stated that at the time of filing the reason for few reports of cows that expressed a protein in their mice by transgenic technology was due to economics and not technology. Applicant argues that Krimpenfort et al (1991) described a male calf that contained a human lactoferrin gene operatively linked to a casein promoter, that Lee et al (1994) indicated that this calf was named "Herman", that in

Biotechnology Newswatch, June 1, 1992 stated that "Herman" was ready to start producing a herd of cows that produce lactoferrin in their milk and that Dutton (May 1, 1996) states that Herman's transgenic offspring are producing human lactoferrin in their milk. Applicant argues that the lag time between reports of "Herman" and the production of lactoferrin in the milk of transgenic cows was due to the length of time necessary to produce calves and have them mature to produce milk. Applicant argues that in the Krimpenfort article above, it is stated that there were in 1991 two options for producing transgenic cattle: by the transfer of microinjected zygotes directly to the recipient cow or by incubating the microinjected zygote to the morula/blastocyst state in vitro. Applicant argues that it is not true that growth to morula/blastocyst stage prior to implantation is necessary. Applicant argues that both skills were known to the artisan at the time of filing. These arguments are not persuasive.

A declaration may be found non-persuasive if the opinions offered by the expert declarant, such as Dr. Bondioli, are refuted by evidence in the art. In the previous office action, and in this office action, it is maintained that the art does not support declarant Bondioli's opinions. The declarant statements were not and are not disregarded, but were, and are, argued against. Declarant's statements that the issues were economic rather than functions are not persuasive against the backdrop that the only cows argued to produce a heterologous protein in their milk were produced by a method that required the incubation of the microinjected zygote to the morula/blastocyst stage prior to transfer to the mother. As stated, the exhibits supplied with the declaration each indicated that for transgenic cows, microinjected zygotes were fertilized in vitro for 7 days or to the morulae/blastocyst stage (Biery et al (Exhibit B), parag. 1, lines 16-19; Bondioli et al (Exhibit C), page 267, parag. 22.1.4; Massey (Exhibit D), page 205, parag. 1, lines 3-4 and Hill et al (Exhibit E), lines 12-13). The evidence in the art and supplied by applicant clearly teaches that incubation to the morula/blastocyst stage is necessary for the production of a transgenic cow, and with the evolution of Herman's cows, which actually produce human lactoferrin in their milk, this

incubation step appears to be a requirement. The facts are that Herman was produce by the incubation of a microinjected zygote to the morula/blastocyst stage prior to transfer to a recipient cow. The cows each of Biery, Bondioli, Massey and Hill of record were not reported to produce a protein in their milk. Thus the evidence does not support the statements of Bondioli that transgenic cows can be produced by direct transfer of the microinjected zygote to a recipient female. Krimpenfort (1991) page 846, col. 1-2, bridg. Parag., discusses the merits of in vivo versus in vitro development of bovine embryos. However, Krimpenfort states direct transfer of microinjected bovine embryos has occurred, not that this lead to the production of transgenic cows expressing a heterologous protein in their milk. Further, in reference 24 and 25 cited by Krimpenfort, Bondioli et al and Massey et al (of record), the bovine embryos were incubated to morula/blastocyst stage prior to transfer to a recipient female. This means that whether incubated in vitro, in culture, or incubated in vivo, in foster oviducts, bovine morula/blastocyst stage embryos were ultimately transferred to the recipient cow for development. The evidence is the art of record does not support the arguments of either applicant or declarant that direct transfer was an enabled method at the time of filing for producing transgenic cow which produce a heterologous protein in their milk. Economic concerns do not lessen the requirement that an invention be enabled at the time of filing.

Applicant's amendments to the claims have overcome the rejection under 35 U.S.C. 112 second paragraph. It is appreciated that applicant recognized the error of citing claim 12 and correct claim 14.

The claims are free of the prior art. At the time of the instant invention, the art did not recognize or suggest the production of protein C in the milk of transgenic non-human mammals, nor did the art recognized the 5'4.2 kb *Sau*3A-*Kpn*1 promoter fragment in the

production of transgenic non-human mammals which expressed a DNA sequence encoding a protein of interest such that the protein could be detected in the milk of the mammal.

Claims 1-4,6-9,11,12,14,16,18,19,22 and 23 are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800

Dr. D. Crouch
October 22, 1997